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Metal-free Syntheses of Oxindole Derivatives via a Benzoylation/ Substitution/Desulfonylation/Cyclization Cascade†

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A benzoylation/substitution/desulfonylation/cyclization cascade reaction giving oxindole derivatives was discovered. The reaction used aromatic aldehydes and *N*-alkyl-*N*-(phenylsulfonyl) methacrylamides as starting materials, and proceeded under mild conditions without using toxic metal catalysts. 3-Methyl-3-aroyloxindole derivatives were formed in good yields.

Oxindole derivatives are important molecules found in a wide range of natural products. They are highly valuable molecules in drug discovery due to their varieties of bioactivities.[1] Many oxindole derivatives have been synthesized and screened, and different biological activities have been reported.[2] Figure 1 shows four representative bioactive oxindole derivatives.[3] These include Convolutamydine A, a natural product with potent activity against leukemia cells.[3a] Also, selective 5-HT_7 receptor antagonists,[3b] an antitumor agent, and selective inhibitors of the plasmodial CDKs are included.[3c-d] Thus, quick syntheses of oxindole derivatives are highly valued in high-throughput screening. Such cascade reactions are greatly desired.

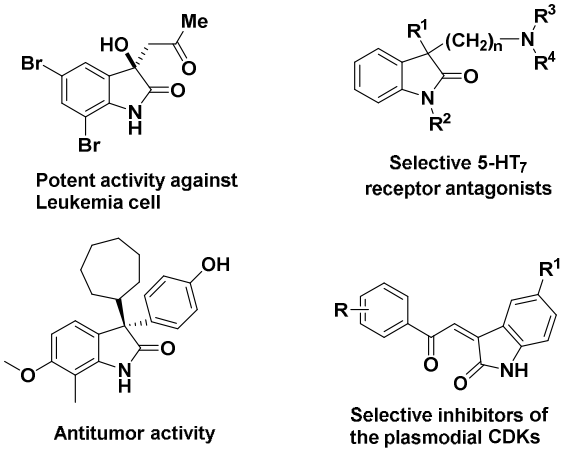
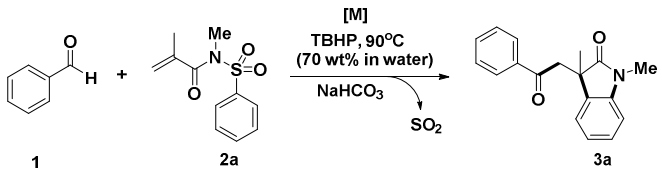


Fig. 1 Biologically active oxindole derivatives

Traditional synthetic methods[4] for generating oxindole derivatives have been supplemented recently by some powerful cascade methods using transitional metal catalysts to carry out oxidative cross couplings of activated alkenes. [5] These methods have attracted a lot of attention. *N*-Alkyl-*N*-(aryl)methacrylamides were normally used as core reactants. By carefully designing their substrate structures, different oxindole derivatives were produced in one-pot cascade sequences under mild conditions. These reactions are atom-economic, highly efficient and environmentally friendly.[6] More recently, another cascade reaction that produces 3-methyl-3-aroyloxindole

Table 1 Optimization of reaction condition [a]



Entry	Cat. (mol%)	Reagent	Solvent	Yield[b] (%)
1	$CuCl_2$	TBHP, $NaHCO_3$	---	35
2		TBHP	---	40
3		TBHP, $NaHCO_3$	---	70
4		DTBP, $NaHCO_3$	---	56
5		$PhI(OAc)_2$ $NaHCO_3$	---	trace
6		TBHP, $NaHCO_3$	DCE	trace
7		TBHP, $NaHCO_3$	Toluene	trace
8		TBHP, $NaHCO_3$	CH_3CN	20
9		TBHP, $NaHCO_3$	EtOAc	53
10		H_2O_2, $NaHCO_3$	---	trace

[a]Reaction conditions: benzaldehyde (5 equiv), *N*-methyl-*N*-(phenylsulfonyl)methacrylamide (1 equiv), aqueous TBHP (*tert*-butyl hydroperoxide,70 wt % in water, 2.5 equiv), H_2O_2 (30 wt % in water, 2.5 equiv), DTBP (*tert*-butyl peroxide, 2.5 equiv), $CuCl_2$ (10 mol%, for entry 1); $NaHCO_3$ (1 equiv), reaction time 18h. [b]Yield is based on reactant **2a**.

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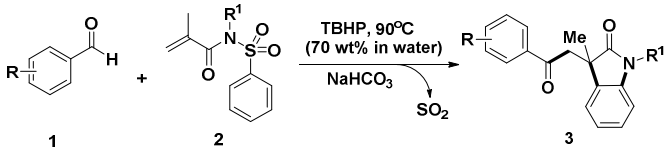
derivatives has quickly drawn attention.[7] Several functionalizations using *N*-alkyl-*N*-(phenylsulfonyl)-methacrylamide as the core reactants have been reported.[7]

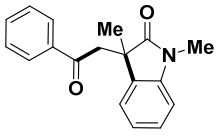
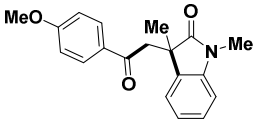
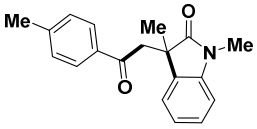
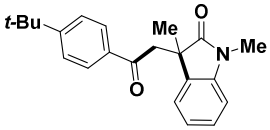
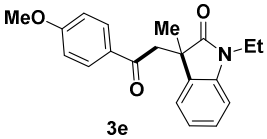
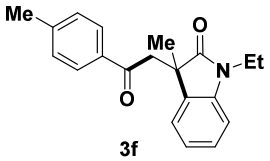
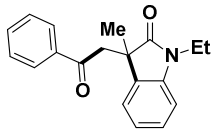
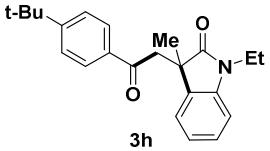
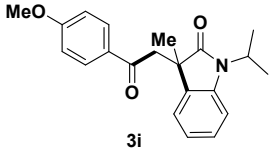
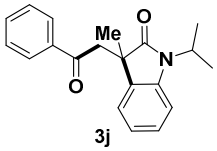
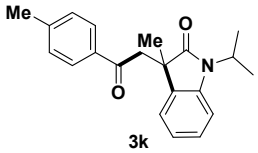
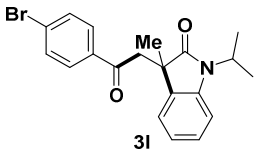
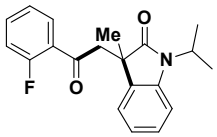
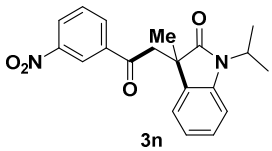
In this paper, a novel cascade reaction involving benzoylation/substitution/desulfonylation/cyclization to produce 3-methyl-3-aroyloxindole derivatives is reported. This process never involves a metal catalyst.

In order to find suitable reaction conditions for this cascade, metal catalysts and radical initiators were initially screened based on previously reported results.[8] *N*-Methyl-*N*-(phenylsulfonyl) methacrylamide and benzaldehyde were used as representative reactants (Table 1) for screening. In entry 1, $CuCl_2$ (10% mol) was used as a catalyst in the presence of TBHP (*tert*-butyl hydroperoxide, 70% in water, 2.5 equiv). Excess benzaldehyde (5 equiv) was used to promote conversion, giving **3a** in a yield of 35%. Using TBHP as the initiator gave about 40% of **3a**. In entry 3, one equivalent of $NaHCO_3$ was also added and **3a** was produced in a good yield of 70%. $NaHCO_3$ can increase the yield greatly; because it may consume the SO_2 released in the reaction.

Table 2 Cascade reactions to generate 3-methyl-3-aroyl oxindole derivatives[a]



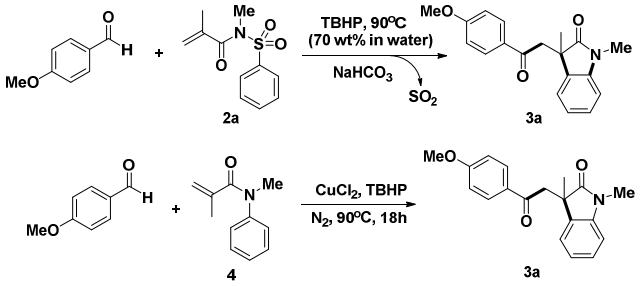
1 2 3

Entry	R	R^1	Product	Yield[b] (%)
1	H	Me	 **3a**	70
2	4-MeO	Me	 **3b**	77
3	4-Me	Me	 **3c**	75
4	4-*t*-Bu	Me	 **3d**	81
5	4-MeO	Et	 **3e**	68
6	4-Me	Et	 **3f**	70
7	H	Et	 **3g**	72
8	4-*t*-Bu	Et	 **3h**	85
9	4-MeO	*i*-Pr	 **3i**	76
10	H	*i*-Pr	 **3j**	74
11	4-CH_3	*i*-Pr	 **3k**	73
12	4-Br	*i*-Pr	 **3l**	70
13	2-F	*i*-Pr	 **3m**	60
14	3-NO_2	*i*-Pr	 **3n**	trace

[a]Reaction conditions: aldehydes (5 equiv), *N*-alkyl-*N*-(phenylsulfonyl) methacrylamides (1 equiv), aqueous TBHP (*tert*-butyl hydroperoxide, 70 wt % in water, 2.5 equiv), $NaHCO_3$ (1equiv), reaction time 18h. [b]Yield calculation is based on reactant **2**.

When TBHP was replaced by DTBP (Di-*tert*-butyl peroxide) in the presence of $NaHCO_3$, **3a** was produced in 56% yield. When $PhI(OAc)_2$ and $NaHCO_3$ were both used, none or only traces of desired **3a** was detected. Using solvents DCE, toluene (entries 6, 7) afforded none or only traces of **3a**, while acetonitrile and EtOAc (entry 8, 9) afforded 20% and 53% of expected product **3a**, respectively. Using H_2O_2 (10% mol) in the presence of $NaHCO_3$ gave only traces of **3a**.

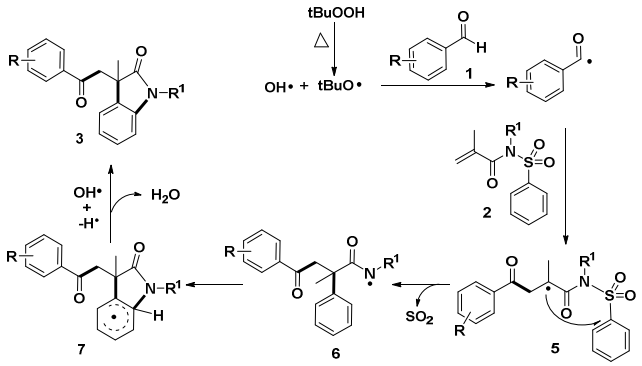
Based on these screening results, the optimized reaction conditions employed were: aldehyde (5 equiv), TBHP (2.5 equiv), 90°C, $NaHCO_3$ (2 equiv), 18h. Under these conditions, fourteen reactions with different substituents were thoroughly studied (Table 2). All these cascade reactions gave 3-methyl-3-aroyloxindole derivatives **3a-m** in good yields except entry 14 using the electron-withdrawing 3-nitrobenzaldehyde as a starting material. This fact indicates that the nitro function may influence radical reaction process, since it didn't give the expected product.



Scheme 1 Comparison reactions

Based on previous reports[7] and our mass spectrometry analysis results, it is obvious that the SO_2 functions were lost during the reaction. No sultams was in the products. To further confirm the product structures; a comparison experiment was conducted (scheme 1). *N*-Methyl-*N*-phenylmethacrylamide was used as a representative starting material to compare with the reaction of **2a**. The ^1H and ^{13}C-NMR of the products from each reaction confirmed that **3a** was produced in both reactions. Obviously, SO_2 is lost in this cascade sequence from **2a**. This conclusion is further supported by the reactions in reference 7. Based on the above, a reaction mechanism is proposed in Scheme 2. When heated, TBHP gives a tBuO• and an •OH radical, which abstract a hydrogen atom from the aryl aldehyde **1** to generate the aroyl radical. This aroyl radical adds to the double bond of *N*-alkyl-*N*-(phenylsulfonyl)acrylamide to give delocalized radical intermediate **5**, which undergoes intramolecular radical substitution at the aromatic ring with loss of SO_2. This forms radical **6**. The addition of resultant radical **6** to the aromatic ring generates radical intermediate **7,** which loses a hydrogen atom to give ketone oxindole derivatives **3** in good yields.

In summary, we have developed a novel, metal-free cascade reaction involving sequential benzoylation/substitution/ desulfonylation/cyclization steps to give 3-methyl-3-aroyloxindole derivatives. The reaction used aromatic aldehydes and *N*-alkyl-*N*-(phenylsulfonyl)methacrylamides as starting materials and proceeded under mild and environmentally friendly conditions to give good yields. This result enriches current methods of generating oxindole derivatives. All of these



Scheme 2 Proposed cascade reaction mechanism

3-methyl-3-aroyloxindole derivatives will be screened soon for biologiocal activities.

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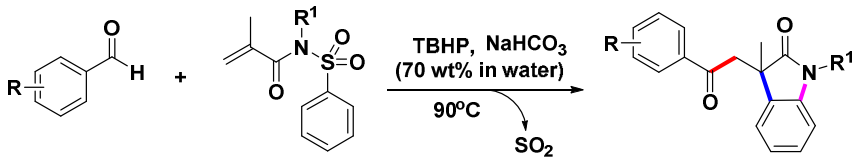
Graphic for Abstract



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